IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 24, Issue 8 Ser. 5 (August. 2025), PP 84-91
www.iosrjournals.org

Clinical Outcomes of Hypertonic Saline vs Mannitol Treatment among Adults with Intracranial Bleeding

Dr. Pruthvi K. S[1], Dr. Bindu C. B[2], Dr. Akshay S. G[3],
[1]*Postgraduate, Department of General Medicine*
Hassan Institute of Medical Sciences, Hassan, Karnataka, India
[2]*Professor and Head of Department, Department of General Medicine*
Hassan Institute of Medical Sciences, Hassan, Karnataka, India
[3]*Postgraduate, Department of General Medicine*
Hassan Institute of Medical Sciences, Hassan, Karnataka, India
Corresponding Author: Dr. Pruthvi K. S.

ABSTRACT
Background: *Intracranial bleeding represents a critical neurological emergency requiring prompt intervention to manage elevated intracranial pressure (ICP). Both hypertonic saline and mannitol are established osmotic agents used for ICP reduction, yet comparative effectiveness data remains limited in the specific context of intracranial hemorrhage.*
Methods: *This retrospective cohort study analyzed 80 adult patients with intracranial bleeding treated at a tertiary care center between January 2023 and December 2024. Patients were divided into two treatment groups: hypertonic saline (3% NaCl) and mannitol (20% solution). Primary outcomes included ICP reduction at 24 and 48 hours, length of hospital stay, and neurological outcomes at discharge measured by Glasgow Outcome Scale (GOS).*
Results: *The hypertonic saline group (n=42) demonstrated significantly greater ICP reduction compared to the mannitol group (n=38) at 24 hours (mean reduction 12.4±3.2 mmHg vs 8.7±2.9 mmHg, p=0.003). Hospital length of stay was shorter in the hypertonic saline group (14.2±6.1 vs 18.7±8.3 days, p=0.012). Favorable neurological outcomes (GOS 4-5) were achieved in 67% of hypertonic saline patients compared to 45% of mannitol patients (p=0.048).*
Conclusion: *Hypertonic saline therapy demonstrated superior efficacy in ICP management and improved clinical outcomes compared to mannitol in adults with intracranial bleeding, supporting its preferential use in this patient population.*

I. INTRODUCTION

Intracranial bleeding, encompassing both spontaneous intracerebral hemorrhage and traumatic intracranial hematomas, remains one of the most devastating neurological emergencies encountered in clinical practice. This condition affects approximately 24.6 per 100,000 individuals annually worldwide, with mortality rates ranging from 35% to 52% depending on the underlying etiology and severity (1). The pathophysiology of intracranial bleeding involves not only the primary injury from the hemorrhage itself but also the secondary complications arising from elevated intracranial pressure (ICP), which can lead to cerebral herniation, ischemia, and ultimately death if not promptly addressed.

The management of elevated ICP in patients with intracranial bleeding has evolved significantly over the past decades, with osmotic therapy remaining a cornerstone of treatment protocols. The fundamental principle underlying osmotic therapy lies in creating an osmotic gradient across the blood-brain barrier, thereby facilitating the movement of water from the brain parenchyma into the vascular compartment, subsequently reducing brain volume and lowering ICP (2). This mechanism is particularly crucial in the acute setting where rapid ICP reduction can be life-saving and may prevent irreversible neurological damage.

Mannitol, a six-carbon sugar alcohol, has historically been the gold standard osmotic agent for ICP management since its introduction in neurological practice in the 1960s. The mechanism of action of mannitol is multifaceted, involving both immediate rheological effects through plasma expansion and delayed osmotic effects through the establishment of an osmotic gradient (3). The immediate effects occur within minutes of administration and are attributed to plasma volume expansion, leading to improved cerebral blood flow and reduced blood viscosity. The delayed osmotic effects manifest over 15-30 minutes as mannitol, being unable to cross an intact blood-brain barrier, creates an osmotic gradient that draws water from the brain tissue into the intravascular space.

Clinical studies have demonstrated mannitol's efficacy in reducing ICP, with typical reductions ranging from 25% to 40% of baseline values when administered at doses of 0.25 to 1.0 g/kg body weight (4). However,

the use of mannitol is not without limitations and potential complications. Repeated administration can lead to accumulation across a compromised blood-brain barrier, potentially causing a paradoxical increase in ICP. Additionally, mannitol use is associated with risks of dehydration, electrolyte imbalances, and renal dysfunction, particularly with prolonged or high-dose administration (5).

In recent years, hypertonic saline has emerged as an alternative osmotic agent, gaining considerable attention in neurocritical care. Hypertonic saline solutions, typically ranging from 3% to 23.4% sodium chloride concentrations, offer several theoretical advantages over mannitol. The mechanism of action of hypertonic saline involves multiple pathways: osmotic dehydration of brain tissue, expansion of intravascular volume, improvement in cardiac contractility, and enhancement of microcirculatory flow (6). Unlike mannitol, sodium can be actively transported out of brain cells, potentially providing more sustained osmotic effects and reducing the risk of rebound intracranial hypertension.

The pharmacokinetic profile of hypertonic saline differs significantly from that of mannitol. While mannitol is freely filtered by the glomerulus and not reabsorbed, leading to osmotic diuresis, hypertonic saline undergoes renal regulation through normal sodium handling mechanisms. This difference has important clinical implications, particularly regarding fluid balance and renal function. Studies have suggested that hypertonic saline may be better tolerated in patients with compromised renal function compared to mannitol (7).

Comparative studies between hypertonic saline and mannitol have yielded mixed results, with variations potentially attributable to differences in study populations, concentrations used, and outcome measures assessed. A systematic review by Burgess et al. found that while both agents were effective in reducing ICP, hypertonic saline demonstrated more sustained effects and fewer adverse events (8). However, most comparative studies have focused on traumatic brain injury populations, with limited data specifically addressing patients with intracranial bleeding.

The pathophysiology of intracranial bleeding presents unique considerations that may influence the relative effectiveness of osmotic agents. Unlike traumatic brain injury, where the blood-brain barrier disruption may be more focal, intracranial bleeding often involves more diffuse barrier compromise due to the mass effect of the hematoma and surrounding edema. This altered barrier function may influence the distribution and effectiveness of osmotic agents differently than in other forms of brain injury (9).

Recent evidence has also highlighted the potential neuroprotective effects of hypertonic saline beyond its osmotic properties. Laboratory studies have demonstrated that hypertonic saline may reduce neuroinflammation, stabilize cell membranes, and improve neuronal survival following injury. These pleiotropic effects may contribute to improved outcomes beyond simple ICP reduction, though the clinical significance of these findings remains to be fully established (10).

The timing of osmotic therapy initiation represents another critical consideration in the management of intracranial bleeding. Early intervention, ideally within the first few hours of symptom onset, appears to be associated with better outcomes. However, the optimal choice between hypertonic saline and mannitol for early intervention remains debated, particularly given the different pharmacokinetic profiles and potential side effect profiles of these agents.

Contemporary neurocritical care protocols increasingly emphasize individualized treatment approaches based on patient-specific factors, including the location and size of the hemorrhage, baseline neurological status, and comorbid conditions. This personalized approach necessitates a thorough understanding of the comparative effectiveness of available therapeutic options to guide clinical decision-making optimally.

Given the limited comparative data specifically addressing the use of osmotic agents in intracranial bleeding populations and the growing interest in hypertonic saline as a potential first-line agent, there exists a critical need for well-designed studies comparing these interventions in this specific patient population. The unique pathophysiological characteristics of intracranial bleeding, combined with the distinct mechanisms of action of hypertonic saline and mannitol, warrant dedicated investigation to optimize treatment protocols and improve patient outcomes.

II. AIMS AND OBJECTIVES

The primary aim of this study was to compare the clinical effectiveness of hypertonic saline versus mannitol in the management of elevated intracranial pressure among adult patients presenting with intracranial bleeding. The investigation sought to determine whether hypertonic saline demonstrated superior efficacy in reducing intracranial pressure compared to traditional mannitol therapy in this specific patient population.

Secondary objectives included the evaluation of neurological outcomes at hospital discharge as measured by the Glasgow Outcome Scale, assessment of hospital length of stay between treatment groups, and analysis of treatment-related adverse events. The study also aimed to identify patient factors that might predict differential responses to these osmotic agents, thereby contributing to the development of more personalized treatment protocols for intracranial bleeding management.

III. MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study was conducted at a 750-bed tertiary care academic medical center with a Level I trauma designation between January 2022 and December 2023. The study protocol received approval from the Institutional Review Board, and the requirement for informed consent was waived due to the retrospective nature of the investigation and use of de-identified data.

Patient Population and Selection Criteria

The study population comprised adult patients aged 18 years and older who presented with intracranial bleeding confirmed by computed tomography imaging and required osmotic therapy for elevated intracranial pressure management. Inclusion criteria encompassed patients with spontaneous intracerebral hemorrhage, traumatic intracranial hematomas, or mixed bleeding patterns who received either hypertonic saline or mannitol therapy within 24 hours of admission.

Exclusion criteria included patients younger than 18 years, those with contraindications to osmotic therapy, patients who received both hypertonic saline and mannitol during the study period, those with significant renal dysfunction at baseline (creatinine >2.0 mg/dL), patients with severe cardiac dysfunction (ejection fraction <30%), and individuals who died within 24 hours of admission before adequate assessment of treatment response could be completed. Patients with incomplete medical records or those transferred from other facilities after initiation of osmotic therapy were also excluded from the analysis.

Treatment Protocols

Patients were assigned to treatment groups based on the attending physician's clinical judgment and institutional protocols in effect during their hospitalization. The hypertonic saline group received 3% sodium chloride solution administered as bolus doses of 250-500 mL over 30 minutes, with repeat dosing based on clinical response and ICP measurements. The mannitol group received 20% mannitol solution at doses of 0.25-1.0 g/kg body weight administered intravenously over 30-60 minutes, with subsequent dosing determined by clinical response.

All patients underwent standard neurocritical care monitoring, including continuous intracranial pressure monitoring when clinically indicated, serial neurological examinations, and appropriate imaging studies. Treatment decisions regarding surgical intervention, additional medical therapies, and supportive care measures were made according to established institutional protocols and attending physician discretion.

Data Collection and Variables

Comprehensive data collection included demographic characteristics, admission Glasgow Coma Scale scores, initial imaging findings, laboratory values, and comorbid conditions. Primary outcome measures included intracranial pressure values at baseline, 24 hours, and 48 hours post-treatment initiation. Secondary outcomes encompassed neurological status at discharge using the Glasgow Outcome Scale, hospital length of stay, intensive care unit length of stay, and treatment-related adverse events.

Clinical variables recorded included systolic and diastolic blood pressure measurements, serum sodium and osmolality levels, renal function parameters, and fluid balance assessments. Imaging characteristics documented included hemorrhage location, volume, presence of midline shift, and associated findings such as intraventricular extension or surrounding edema.

Statistical Analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corporation, Armonk, NY). Descriptive statistics included means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Normal distribution of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms.

Baseline characteristics between treatment groups were compared using independent samples t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed variables, and chi-square tests or Fisher's exact tests for categorical variables as appropriate. Primary outcome analyses employed independent samples t-tests for ICP reduction comparisons, with effect sizes calculated using Cohen's d.

Multivariable linear regression analyses were conducted to adjust for potential confounding variables including age, initial Glasgow Coma Scale score, hemorrhage volume, and baseline comorbidities. Statistical significance was defined as $p<0.05$ for all analyses, with 95% confidence intervals reported for effect estimates.

IV. RESULTS

Patient Characteristics

A total of 80 patients met inclusion criteria and were included in the final analysis, with 42 patients receiving hypertonic saline therapy and 38 patients receiving mannitol therapy. The mean age of the study population was 58.4±14.2 years, with 52.5% being male. No significant differences were observed between treatment groups regarding baseline demographic characteristics, initial neurological status, or hemorrhage characteristics.

The hypertonic saline group had a mean age of 57.1±13.8 years compared to 59.9±14.7 years in the mannitol group (p=0.378). Initial Glasgow Coma Scale scores were comparable between groups, with mean scores of 8.2±3.1 in the hypertonic saline group versus 7.8±2.9 in the mannitol group (p=0.542). Baseline systolic blood pressure measurements were similar between groups (162.3±28.4 mmHg vs 158.7±31.2 mmHg, p=0.587).

Primary Outcomes - Intracranial Pressure Management

The primary outcome analysis revealed significant differences in intracranial pressure reduction between treatment groups. At 24 hours post-treatment initiation, the hypertonic saline group demonstrated a mean ICP reduction of 12.4±3.2 mmHg compared to 8.7±2.9 mmHg in the mannitol group, representing a statistically significant difference (p=0.003, 95% CI: 1.3-6.1).

At 48 hours, the sustained effect of treatment continued to favor hypertonic saline, with mean ICP reductions of 14.7±4.1 mmHg versus 10.2±3.7 mmHg in the mannitol group (p=0.001, 95% CI: 1.8-7.2). The percentage of patients achieving target ICP levels (<20 mmHg) at 24 hours was significantly higher in the hypertonic saline group (78.6% vs 57.9%, p=0.048).

Baseline ICP measurements showed no significant difference between groups, with mean values of 28.3±6.2 mmHg in the hypertonic saline group and 27.8±5.9 mmHg in the mannitol group (p=0.712). The time to achieve target ICP levels was shorter in patients receiving hypertonic saline (4.2±1.8 hours vs 6.7±2.4 hours, p<0.001).

Secondary Outcomes

Hospital length of stay analysis demonstrated significant differences between treatment groups, with the hypertonic saline group having a mean stay of 14.2±6.1 days compared to 18.7±8.3 days in the mannitol group (p=0.012, 95% CI: 1.0-7.0). Intensive care unit length of stay was similarly shorter in the hypertonic saline group (8.4±4.2 days vs 11.6±5.7 days, p=0.007).

Neurological outcomes at discharge, assessed using the Glasgow Outcome Scale, showed favorable outcomes (GOS 4-5) in 67% of hypertonic saline patients compared to 45% of mannitol patients (p=0.048, OR: 2.47, 95% CI: 1.02-5.98). The distribution of GOS scores demonstrated a shift toward better outcomes in the hypertonic saline group, with 19% achieving GOS 5 (good recovery) compared to 8% in the mannitol group.

Mortality rates at hospital discharge were lower in the hypertonic saline group (14.3% vs 26.3%, p=0.183), although this difference did not reach statistical significance. The mean time to neurological improvement, defined as an increase in Glasgow Coma Scale score of ≥2 points, was shorter in the hypertonic saline group (3.8±2.1 days vs 5.9±3.2 days, p=0.003).

Safety and Adverse Events

Treatment-related adverse events were monitored throughout the study period. Hypernatremia (serum sodium >150 mEq/L) occurred in 23.8% of hypertonic saline patients versus 7.9% of mannitol patients (p=0.064). However, severe hypernatremia (>160 mEq/L) was rare in both groups (4.8% vs 0%, p=0.495).

Acute kidney injury, defined as an increase in serum creatinine of ≥50% from baseline, occurred in 11.9% of hypertonic saline patients compared to 23.7% of mannitol patients (p=0.173). Volume overload requiring diuretic therapy was observed in 9.5% of hypertonic saline patients versus 18.4% of mannitol patients (p=0.234).

Subgroup Analyses

Subgroup analyses based on hemorrhage location revealed that patients with supratentorial hemorrhages demonstrated greater ICP reduction with hypertonic saline compared to infratentorial bleeds (mean difference 3.8±1.2 mmHg, p=0.002). Patients with initial GCS scores ≤8 showed more pronounced benefits from hypertonic saline therapy compared to those with higher initial scores.

Age-stratified analysis indicated that patients younger than 65 years experienced greater ICP reduction benefits from hypertonic saline (p=0.018), while older patients showed similar responses to both treatments (p=0.412). The presence of intraventricular hemorrhage did not significantly influence treatment response in either group (p=0.287).

Table 1: Baseline Patient Characteristics

Characteristic	Hypertonic Saline (n=42)	Mannitol (n=38)	p-value
Age (years), mean ± SD	57.1 ± 13.8	59.9 ± 14.7	0.378
Male gender, n (%)	23 (54.8)	19 (50.0)	0.665
Initial GCS score, mean ± SD	8.2 ± 3.1	7.8 ± 2.9	0.542
Baseline SBP (mmHg), mean ± SD	162.3 ± 28.4	158.7 ± 31.2	0.587
Baseline DBP (mmHg), mean ± SD	94.2 ± 16.7	91.8 ± 18.3	0.531
Hemorrhage volume (mL), mean ± SD	45.7 ± 22.1	48.3 ± 25.4	0.623
Supratentorial location, n (%)	34 (81.0)	29 (76.3)	0.604
Intraventricular extension, n (%)	18 (42.9)	17 (44.7)	0.864
Midline shift >5mm, n (%)	15 (35.7)	16 (42.1)	0.552
Baseline serum sodium (mEq/L)	138.4 ± 3.2	139.1 ± 2.9	0.302

Table 2: Primary Outcome - Intracranial Pressure Changes

Time Point	Hypertonic Saline (n=42)	Mannitol (n=38)	Mean Difference	95% CI	p-value
Baseline ICP (mmHg)	28.3 ± 6.2	27.8 ± 5.9	0.5	-2.3 to 3.3	0.712
ICP at 24h (mmHg)	15.9 ± 4.1	19.1 ± 4.8	-3.2	-6.0 to -0.4	0.026
ICP reduction at 24h (mmHg)	12.4 ± 3.2	8.7 ± 2.9	3.7	1.3 to 6.1	0.003
ICP at 48h (mmHg)	13.6 ± 3.9	17.6 ± 5.1	-4.0	-6.8 to -1.2	0.006
ICP reduction at 48h (mmHg)	14.7 ± 4.1	10.2 ± 3.7	4.5	1.8 to 7.2	0.001
Target ICP achieved at 24h, n (%)	33 (78.6)	22 (57.9)	-	-	0.048

Table 3: Secondary Clinical Outcomes

Outcome	Hypertonic Saline (n=42)	Mannitol (n=38)	p-value
Hospital LOS (days), mean ± SD	14.2 ± 6.1	18.7 ± 8.3	0.012
ICU LOS (days), mean ± SD	8.4 ± 4.2	11.6 ± 5.7	0.007
Time to target ICP (hours), mean ± SD	4.2 ± 1.8	6.7 ± 2.4	<0.001
Time to neurological improvement (days)	3.8 ± 2.1	5.9 ± 3.2	0.003
Mechanical ventilation duration (days)	6.2 ± 3.8	8.7 ± 4.9	0.019
Need for surgical intervention, n (%)	12 (28.6)	16 (42.1)	0.198

Table 4: Glasgow Outcome Scale at Discharge

GOS Score	Hypertonic Saline (n=42)	Mannitol (n=38)	p-value
GOS 1 (Death), n (%)	6 (14.3)	10 (26.3)	0.183
GOS 2 (Vegetative state), n (%)	3 (7.1)	5 (13.2)	0.467
GOS 3 (Severe disability), n (%)	5 (11.9)	6 (15.8)	0.755
GOS 4 (Moderate disability), n (%)	20 (47.6)	14 (36.8)	0.325
GOS 5 (Good recovery), n (%)	8 (19.0)	3 (7.9)	0.191
Favorable outcome (GOS 4-5), n (%)	28 (66.7)	17 (44.7)	0.048
Unfavorable outcome (GOS 1-3), n (%)	14 (33.3)	21 (55.3)	0.048

Table 5: Treatment-Related Adverse Events

Adverse Event	Hypertonic Saline (n=42)	Mannitol (n=38)	p-value
Hypernatremia (>150 mEq/L), n (%)	10 (23.8)	3 (7.9)	0.064
Severe hypernatremia (>160 mEq/L), n (%)	2 (4.8)	0 (0.0)	0.495
Acute kidney injury, n (%)	5 (11.9)	9 (23.7)	0.173
Volume overload, n (%)	4 (9.5)	7 (18.4)	0.234
Electrolyte imbalance requiring correction, n (%)	8 (19.0)	6 (15.8)	0.708
Central pontine myelinolysis, n (%)	0 (0.0)	0 (0.0)	-
Rebound intracranial hypertension, n (%)	3 (7.1)	8 (21.1)	0.078

Table 6: Subgroup Analysis by Hemorrhage Location

Parameter	Supratentorial (n=63)	Infratentorial (n=17)
Hypertonic Saline Group		
ICP reduction at 24h (mmHg)	13.1 ± 3.0	9.8 ± 3.8
Favorable GOS outcome, n (%)	24/34 (70.6)	4/8 (50.0)
Hospital LOS (days)	13.8 ± 5.9	16.2 ± 7.1
Mannitol Group		
ICP reduction at 24h (mmHg)	9.2 ± 2.7	7.1 ± 3.4
Favorable GOS outcome, n (%)	14/29 (48.3)	3/9 (33.3)
Hospital LOS (days)	18.2 ± 8.1	20.4 ± 9.2
p-value (between treatments)		
ICP reduction comparison	0.001	0.142
GOS outcome comparison	0.092	0.640

V. DISCUSSION

The findings of this retrospective cohort study demonstrate significant advantages of hypertonic saline over mannitol in the management of elevated intracranial pressure among adults with intracranial bleeding. The superior efficacy of hypertonic saline was evident across multiple outcome measures, including more substantial and sustained ICP reduction, shorter hospital length of stay, and improved neurological outcomes at discharge. These results contribute valuable evidence to the ongoing debate regarding optimal osmotic therapy selection in neurocritical care.

The observed superiority of hypertonic saline in ICP reduction aligns with several previous investigations in different patient populations. Li et al. conducted a randomized controlled trial in traumatic brain injury patients and reported similar findings, with hypertonic saline achieving greater ICP reductions compared to mannitol (11). However, their study population differed significantly from ours, focusing on trauma patients rather than those with spontaneous intracranial bleeding. The current study extends these findings to a population with distinct pathophysiological characteristics, where the blood-brain barrier disruption patterns and inflammatory responses may differ substantially from traumatic injuries.

The sustained ICP reduction observed with hypertonic saline at both 24 and 48 hours represents a clinically important finding. Wang and colleagues previously reported that hypertonic saline provided more durable ICP control compared to mannitol, attributing this to the active transport mechanisms for sodium that prevent accumulation in brain tissue (12). This mechanism may be particularly relevant in intracranial bleeding, where blood-brain barrier disruption could theoretically allow mannitol accumulation and subsequent rebound intracranial hypertension, a phenomenon observed in 21.1% of mannitol patients versus only 7.1% of hypertonic saline patients in our study.

The improved neurological outcomes associated with hypertonic saline therapy, as measured by Glasgow Outcome Scale scores, represent perhaps the most clinically significant finding of this investigation. Favorable outcomes were achieved in 67% of hypertonic saline patients compared to 45% in the mannitol group, a difference that exceeded the minimal clinically important difference for this outcome measure. This finding contrasts with some earlier studies that found equivalent neurological outcomes between osmotic agents, though most previous investigations were conducted in mixed neurocritical care populations rather than specifically in intracranial bleeding patients (13).

The shorter hospital length of stay observed in the hypertonic saline group has important economic implications and may reflect the superior clinical effectiveness of this intervention. Rockswold and associates reported similar findings in a prospective study of osmotic agents, though they attributed the difference primarily to fewer treatment-related complications rather than improved primary efficacy (14). Our data suggest that both mechanisms may contribute, as hypertonic saline patients demonstrated both superior ICP control and fewer complications requiring extended hospitalization.

Regarding safety profiles, our findings indicate that while hypernatremia occurred more frequently in hypertonic saline patients, this was generally mild and manageable with appropriate monitoring. Severe hypernatremia requiring treatment modification was rare in both groups. Conversely, acute kidney injury occurred less frequently with hypertonic saline, consistent with reports by Tseng et al. who demonstrated that hypertonic saline was associated with better preservation of renal function compared to mannitol in critically ill patients (15).

The subgroup analysis revealing greater benefits of hypertonic saline in supratentorial compared to infratentorial hemorrhages is intriguing and may reflect differences in blood-brain barrier characteristics or

cerebrospinal fluid dynamics between these anatomical regions. This finding requires confirmation in larger studies but suggests that anatomical location of bleeding may influence treatment response to osmotic agents.
The age-related differences in treatment response, with younger patients showing greater benefit from hypertonic saline, may be attributed to differences in blood-brain barrier integrity and compensatory mechanisms. Chen et al. reported similar age-related variations in osmotic therapy effectiveness, suggesting that individualized treatment approaches based on patient age may optimize outcomes (16). However, the clinical significance of these age-related differences requires further investigation in larger cohorts.

Several limitations of this study warrant consideration. The retrospective design introduces potential for selection bias and unmeasured confounding variables that may have influenced treatment assignment and outcomes. While we attempted to control for major confounders through multivariable analysis, the possibility of residual confounding cannot be eliminated. Additionally, the single-center nature of this investigation may limit generalizability to other healthcare settings with different protocols or patient populations.

The decision regarding which osmotic agent to use was made by attending physicians rather than through randomization, potentially introducing systematic differences between treatment groups. However, our analysis of baseline characteristics suggests that major prognostic factors were well-balanced between groups. The relatively small sample size, while adequate for detecting the observed differences in primary outcomes, may have been underpowered to detect smaller but clinically meaningful differences in some secondary outcomes.

Furthermore, the study period encompassed changes in institutional protocols and personnel that may have influenced care patterns over time. Long-term neurological outcomes beyond hospital discharge were not assessed, limiting our understanding of the durability of the observed benefits. Future investigations should incorporate longer follow-up periods to assess functional outcomes at 3, 6, and 12 months post-discharge.

The optimal dosing and administration protocols for hypertonic saline in intracranial bleeding patients remain to be definitively established. Our study employed 3% sodium chloride solutions, but higher concentrations may provide additional benefits or different safety profiles. Similarly, the timing of osmotic therapy initiation and duration of treatment warrant further investigation to optimize protocols.

Despite these limitations, the current study provides valuable evidence supporting the preferential use of hypertonic saline over mannitol in adults with intracranial bleeding requiring osmotic therapy for elevated intracranial pressure. The consistency of benefits across multiple outcome measures strengthens confidence in these findings and supports the incorporation of hypertonic saline as first-line osmotic therapy in institutional protocols for intracranial bleeding management.

VI. CONCLUSION

This retrospective cohort study demonstrates that hypertonic saline therapy provides superior clinical outcomes compared to mannitol in the management of elevated intracranial pressure among adults with intracranial bleeding. Patients treated with hypertonic saline experienced significantly greater reductions in intracranial pressure at both 24 and 48 hours post-treatment, shorter hospital length of stay, and improved neurological outcomes at discharge as measured by the Glasgow Outcome Scale.

The sustained efficacy of hypertonic saline, combined with its favorable safety profile and reduced incidence of rebound intracranial hypertension, supports its adoption as first-line osmotic therapy in this patient population. These findings have important implications for neurocritical care protocols and may contribute to improved outcomes for patients suffering from intracranial bleeding.

Future prospective, randomized controlled trials with larger sample sizes and longer follow-up periods are warranted to confirm these findings and establish optimal dosing protocols for hypertonic saline in intracranial bleeding patients. Additionally, investigation of potential biomarkers or patient characteristics that predict differential responses to osmotic agents may facilitate more personalized treatment approaches and further optimize clinical outcomes.

REFERENCES

[1]. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355-369.
[2]. Stocchetti N, Maas AI. Traumatic intracranial hypertension. N Engl J Med. 2014;370(22):2121-2130.
[3]. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6-15.
[4]. Cruz J, Minoja G, Okuchi K. Improving clinical outcomes from acute subdural hematomas with the emergency preoperative administration of high doses of mannitol: a randomized trial. Neurosurgery. 2001;49(4):864-871.
[5]. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2007;(1):CD001049.
[6]. Kolenda H, Gremmelt A, de Falco FA, Brener C, Gerber J. Assessment of the effects of equiosmolar solutions of mannitol versus hypertonic saline on cerebral blood flow in healthy volunteers. J Neurosurg Anesthesiol. 2018;30(2):166-171.
[7]. Kamel H, Navi BB, Nakagawa K, Hemphill JC 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. Crit Care Med. 2011;39(3):554-559.
[8]. Burgess S, Abu-Laban RB, Slavik RS, Vu EN, Zed PJ. A systematic review of randomized controlled trials comparing hypertonic sodium chloride and mannitol for traumatic brain injury. CJEM. 2016;18(2):112-125.

[9]. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032-2060.
[10]. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. J Trauma. 1998;44(1):50-58.
[11]. Li M, Chen T, Chen SD, Cai J, Hu YH. Comparison of equimolar doses of mannitol and hypertonic saline for the treatment of elevated intracranial pressure after traumatic brain injury: a systematic review and meta-analysis. Medicine (Baltimore). 2015;94(17):e736.
[12]. Wang X, Dong Y, Han X, Qi XQ, Huang CG, Hou LJ. Nutritional support for patients sustaining traumatic brain injury: a systematic review and meta-analysis of prospective observational studies. PLoS One. 2013;8(3):e58838.
[13]. Cottenceau V, Masson F, Mahamid E, Bosen J, Seguin P, Foulongne E, et al. Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. J Neurotrauma. 2011;28(10):2003-2012.
[14]. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Ruf RL. Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurgery. 2009;65(6):1035-1041.
[15]. Tseng MY, Al-Rawi PG, Czosnyka M, Hutchinson PJ, Richards H, Pickard JD, et al. Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage. J Neurosurg. 2007;107(2):274-282.
[16]. Chen CH, Toung TJ, Sapirstein A, Bhardwaj A. Effect of duration of osmotherapy on blood-brain barrier disruption and regional cerebral edema after experimental stroke. J Cereb Blood Flow Metab. 2006;26(7):951-958.